Remarks

Status of the Claims

Claims 3-30 have been withdrawn from consideration, as being directed to non-elected subject matter. Claims 1 and 2 are pending.

Rejection Pursuant to 35 U.S.C. §101

Reconsideration is requested of the rejection of claims 1-2 under 35 U.S.C. §101 for not being supported by either a specific and substantial asserted utility or a well-established utility. More specifically, the Office asserted that factor H related protein 5 (FHR-5), fragments thereof, and sequences with at least 90% identity to FHR-5 lack utility. Applicants respectfully disagree.

As stated in the specification, FHR-5 has been widely detected in vivo in association with the terminal C5b-9 complexes and appears to co-localize with these complexes in both normal and pathological human tissues (page 9, lines 16-19). It is further stated that "FHR-5 is useful as a marker for the terminal C5b-9 complex" (page 9, lines 18-19). Furthermore, it is stated in the specification that "substantially isolated FHR-5, or a substantially identical protein with the same epitope, can be used to generate antibodies which are useful for the identification of activated complement, but which do not cross-react with normal human serum" (page 15, lines 16-19).

The relevance of FHR-5 can be understood in the context of C5b-9 function. The formation of a macromolecular complex of complement proteins known as the membrane attack complex (MAC or C5b-9) is a terminal step in the activation of complement and disrupts the cellular lipid bilayer, leading to cell death. As complement is activated in immune responses against pathogens and also in a number of autoimmune disorders, the presence of the C5b-9 complex indicates the extent of cell death and/or potential damage to tissue(s) where C5b-9 localizes.

Accordingly, as a marker for C5b-9, FHR-5 protein has a specific and substantial asserted utility. In addition, FHR-5 has a specific and substantial utility in the production of anti-FHR-5 antibodies that are useful for identification of activated complement.

Applicants further submit that sequences which exhibit at least 90% sequence identity to FHR-5 protein have the same utility as the FHR-5 protein, i.e. they can be used as markers for C5b-9 complex and in generation of antibodies that are useful for identification of activated complement but that do not cross-react with normal human serum. The correlation of function and sequence identity is discussed below, under the 35 U.S.C. §112 rejection.

It was further stated in the Office action that there is no asserted utility for the disclosed C5b-9 complex. Applicants note that the function of the C5b-9 complex is well established. More importantly, Applicants are not trying to establish a new utility for the C5b-9 complex; rather, a utility for the FHR-5 protein in the context of the C5b-9 complex is established.

Further to the above discussion and as discussed in MPEP §2107,

> If the applicant has asserted that the claimed invention is *useful for any particular practical purpose* (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (Emphasis added.)

In view of the foregoing, Applicants respectfully traverse this basis for rejection and request its reconsideration and withdrawal.

Rejection Pursuant to 35 U.S.C. §112, 1st ¶

Reconsideration is requested of the rejection of claims 1-2 under 35 U.S.C. §112, as failing to comply with the written description requirement.

Claim 1 was rejected for being directed in part to an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 2. In particular, it was stated in the Office action that there is no description of the differences brought about by a percent identity difference that would result in a biologically active protein. It was further stated that there is no apparent discussion in the specification as to what part(s) of protein would have to remain for a proper function of the protein since there is no discussion regarding the actual function of the protein, fragments thereof or sequences with at least 90% sequence identity to SEQ ID NO: 2. Claim 2

was rejected as being directed to a substantially purified FHR-5 fragment, which comprises a fragment of SEQ ID NO: 2.

To satisfy the written description requirement, the specification need only convey "with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." MPEP § 2163.02; *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). (Emphasis added.)

As discussed in the specification, the techniques for determining sequence identity and generating sequences with a particular % of sequence identity are well known in the art (see also, page 13, lines 21-36, and page 14, lines 1-8). In addition, the specification details that for purposes of the present invention, the sequence identity is measured by the number of identical amino acids in the sequences when the sequence of the protein is aligned with SEQ ID NO: 2 and gaps are introduced in order to produce the greatest number of amino acid matches (page 13, lines 8-13). It is further specified that sequence identity of at least 90, 95 or 98% means having about 495, 523 or 539 matching amino acids identical, respectively (page 13, lines 8-20). The specification also states that the amino acid sequences with at least 90% sequence identity to SEQ ID NO: 2 are capable of associating with activated complement, which as described in the application is a function of SEQ ID NO: 2 (FHR-5). Accordingly, in addition to a high structural identity, the amino acid sequences with at least 90% identity are also the functional equivalents of FHR-5.

Furthermore, it is known in the art that conservative amino acid substitutions can be introduced into a protein without affecting its function (see also pages 11-14 of the application). Accordingly, using such substitutions, it is possible to have even lower amino acid sequence identity while retaining the same protein structure and function. Table 1 lists a number of conservative substitutions that can be performed. For example, alanine can be substituted with glycine or serine, arginine can be substituted with lysine, etc. Hence, one skilled in the art can readily design a protein that is 90% identical to FHR-5. Furthermore, determining whether such

designed protein has the same function as FHR-5 can be readily determined using, e.g., in vitro binding studies as described in Example 3.

With regard to the FHR-5 fragment, the specification discloses that it is a polypeptide that comprises a fragment of SEQ ID NO: 2, binds to C3b, and is recognized by the monoclonal antibody K2.254 when associated with activated complement (page 14, lines 32-36). Applicants submit that these characteristics are sufficient to show possession of the invention.

As stated in MPEP 2163:

> Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119, S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406, *Amgen, Inc. v. Chugai Pharmaceutical* , 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). (Emphasis added.)

Applicants submit that the specification describes distinguishing identifying characteristics of amino acid sequences having at least 90% sequence identity to SEQ ID NO: 2 and FHR-5 fragments comprising a fragment of SEQ ID NO: 2 in a manner sufficient to show that Applicants were in possession of the claimed invention at the time of filing. Accordingly, the description of amino acid sequences having at least 90% sequence identity to SEQ ID NO: 2 and FHR-5 fragments comprising a fragment of SEQ ID NO: 2 satisfies the written description requirement of 35 U.S.C. § 112, first paragraph.

Claims 1-2 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Firstly, in view of the 35 U.S.C. § 101 rejection, the Office further stated that a skilled artisan would not know how to make and/or use the claimed invention due to the lack of utility of above-mentioned sequences.

Applicants submit that the specification specifically discloses utility for SEQ ID NO: 2, a sequence with at least 90% sequence identity to SEQ ID NO: 2, and a fragment of SEQ ID NO: 2 as discussed in detail above. Accordingly, Applicants respectfully request that the enablement rejection be withdrawn in view of the utility arguments discussed above. Furthermore, the present application contains working examples that describe how to utilize the above-mentioned sequences.

Secondly, the Office rejected claim 1 for lack of enablement with regard to "an amino acid sequence having at least 90% identity to SEQ ID NO: 2". As one of the examples in support of the argument, the Office cited Skolnick et al., who stated that protein structure by itself is insufficient for annotating a number of functional classes and also for the specific details of protein function. However, the protein structure-function relationship has been taken out of context in this case. Skolnick states that it can be difficult to determine a function of a protein based on a new genetic sequence since a protein can have more than one function and a new sequence may not necessarily exhibit high sequence homology with previously identified sequences. Skolnick's discussion is not applicable to the present invention since the FHR-5 protein sequence, the DNA sequence encoding it, and FHR-5 function have been established. Furthermore, it is well established in the art that an amino acid identity of 90% is a very high identity, and a skilled artisan would not expect such sequence to have a different function than the protein to which it is 90% identical. In addition, one skilled in the art can readily determine which amino acids may be substituted in order to preserve 90% identity and function of the protein. By way of example, alanine scans can be used to determine which amino acids are essential structural and/or functional features of the protein and which amino acids can be substituted without affecting these characteristics.

The Office also noted the Brenner article (Trends in Genetics 15, 132-133, 1999); however, this article discusses structure-function relationship in terms of gene superfamilies. Considering that there are about 1000 such superfamilies and based on a vast number of genes in nature, these superfamilies include genes that need only be minimally related, either structurally

or functionally. Hence, the discussion in the Brenner article is not applicable to a case of two amino acid sequences that exhibit 90% sequence identity and have the same function.

The Office further cites the Bork et al. article, which discloses that "the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database," and that such concerns are also echoed by Doerks et al. and Smith et al. Again, Applicants submit that while it may be difficult to predict a function *of a new sequence based on a comparison with a sequence database*, designing a protein which is 90% identical to a protein whose sequence and function are established is readily within the knowledge of a skilled artisan. Lastly, Bork et al. state that a function of a new protein can be assigned "based on structural similarity of a small domain of the new protein to a small domain of a known protein." Applicants note that Bork et al. refer to assigning function based on a sequence similarity of *a small domain of the new protein to a* ***small domain*** *of a known protein*, whereas the present invention discloses a sequence having ***90% identity*** to FHR-5.

Accordingly, Applicants respectfully traverse this basis for rejection and request its reconsideration and withdrawal.

Rejection Pursuant to 35 U.S.C., 2nd Paragraph

Claims 1-2 were rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 was rejected for the recitation of the phrase "an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 2." Claim 2 was rejected for using the term "fragment of SEQ ID NO: 2."

Applicants note that 35 U.S.C. 112, second paragraph requires claims to "set out and circumscribe a particular subject matter with a *reasonable* degree of clarity and particularity." MPEP §2173.02 (emphasis added).

As the court in *In re Borkowski and Van Venrooy* stated,

> If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends the claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention. 164 U.S.P.Q. 642, 645-46 (C.C.P.A. 1970).

Applicants are thus not required to define the intended sequences with 90% identity to FHR-5, as long as the intended scope of the subject matter is clear. It is not necessary to identify each intended sequence with a sequence identification number to satisfy the requirements of 35 U.S.C. § 112, second paragraph. The specification defines how to identify and how to design sequences with 90% identity to FHR-5. The specification further identifies the computer programs that may be used to determine sequence identity, align sequences, etc. (page 13, lines 21-36, and page 14, lines 1-8). As mentioned above, alanine scans and a number of other techniques may be used to determine which amino acids are necessary and which may be substituted in order to achieve 90% sequence identity and retain the same protein function.

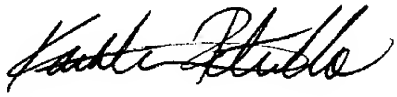
In general, to determine whether claim language is sufficiently definite, the claims must be examined to see whether the metes and bounds of the invention can adequately be determined from the claim language; that is, whether a person of ordinary skill would have any difficulty in ascertaining whether a particular combination falls within or outside the claimed combination. *In re Goffe*, 526 F.2d 1393, 1397-1398 (CCPA 1975). Applicants submit that one of ordinary skill in the art can readily determine whether a particular sequence falls within the definition of an amino acid sequence that is 90% identical to SEQ ID NO: 2.

As discussed above, an FHR-5 fragment is a polypeptide that comprises a fragment of SEQ ID NO: 2, binds to C3b, and is recognized by monoclonal antibody K2.254 when associated with activated complement. Thus, Applicants note that the FHR-5 fragment needs to contain a part of the disclosed SEQ ID NO: 2. Whether such a fragment binds to C3b and is recognized by the K2.254 antibody can readily be determined, e.g., as described in Examples 2 and 3. Accordingly, one of ordinary skill in the art can readily determine whether a particular polypeptide falls within the definition of the FHR-5 fragment.

In view of the above arguments, Applicants respectfully traverse this basis for rejection and request its reconsideration and withdrawal.

The Commissioner is hereby authorized to charge any deficiency or overpayment of the required fee to Deposit Account No. 19-1345.

Respectfully submitted,



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